PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
B01L 3/00, G01N 21/03	A1	WO 94/21379
		(43) International Publication Date: 29 September 1994 (29.09.94)

(21) International Application Number: PCT/CA94/00158

(22) International Filing Date: 11 March 1994 (11.03.94)

(30) Priority Data:
08/032,045 16 March 1993 (16.03.93) US

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(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

(54) Title: ENHANCED MICROTITRE PLATE AND IMMUNOASSAYS CONDUCTED THEREIN

(57) Abstract

A microtitre plate containing a plurality of wells for conducting immunoassays wherein one or more of the sides, bottom and lid walls of each well are formed with a reflective, metallized surface. The surface may be an inner coating on the walls of clear or opaque plates, or an outer coating on the walls of clear plates. Alternatively, the plate may be formed, for example, by stamping from a reflective metal material. Improved sensitivity in photometric detection results from photon emitting immunoassays conducted inthe plate.

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"ENHANCED MICROTITRE PLATE AND IMMUNOASSAYS CONDUCTED THEREIN"

FIELD OF THE INVENTION

This invention relates to microtitre plates and immunogenic assays conducted therein.

BACKGROUND OF THE INVENTION

Microtitre plates are moulded plastic plates or trays having a plurality of depressions or wells in which chemical and biological tests are carried out. Immunogenic assays involving an antibody-antigen reaction to detect an antibody or antigen in biological materials such as serum are most commonly performed in microtitre plates. Colorimetric immunoassays are widely used, the most common type being an ELISA (enzyme-linked immunosorbent assay) method. This technique is an enzyme immunoassay used for the detection of antibodies or antigens. Antigens are immobilized on the surfaces of the wells of the microtitre plates, following which, the sample to be assayed for particular antibodies, typically serum, is added to the wells in specific assay dilutions. This step is followed by the immuno detection of the antibody/antigen complexes, usually by photometrically measuring an enzymatically labelled colour-forming immune complex. In colorimetric immunoassays, a source of incident light is directed onto or through the assay reagents (typically in a clear multi-well microtitre plate). A portion of the radiant energy of the incident beam is absorbed by a component the assay. The light which is transmitted from the assay is detected by a suitable photometer to provide a measurement of the concentration of a component of the assay. Colorimetric immunoassays are photon absorbing assays.

Other photometric assay techniques performed in microtitre plates are termed photon emitting immunoassays. These include chemiluminescent, bioluminescent and fluorescent immunoassays. In these assays photons are emitted, for example as a result of the action of an enzyme, or through the use of particular photon emitting labels.

Emitted photons are detected by suitable photometric devices such as luminometers or fluorometers.

Immunoassays are typically conducted in microtitre plates. Such plates are typically made of a light transmitting plastic polymer such as polystyrene or polyvinylchoride. It is usually important that the microtitre plate be formed from a light transmitting plastic since reading of the assay results is typically done through the contents in the wells, particularly for colorimetric immunoassays.

In the case of photon emitting immunoassays, the microtitre plates may be made of opaque plastic, such as black or white polystyrene, in order to reduce "cross-talk" in photometrically reading the results from well to well (i.e. to reduce interference caused by stray photons). While cross-talk may be lessened by such opaque microtitre plates, the sensitivity of the results is lessened. For instance, black plates absorb some of the photons being emitted from the plates while white plates simply scatter the photons.

Japanese Patent 61-215947 teaches that the optical interference in colorimetric immunoassays carried out in transparent microtitre plates can be reduced by constructing wells optically independently with an opaque layer on the well walls.

An immunoassay technique of greater sensitivity often resorted to is a radioimmunoassay (RIA). However, this technique is costly both in time and equipment needs as it involves the use of radioactive materials. These materials require special handling and licenses from the time they are ordered until they are safely stored at a radioactive waste site. However, even with the drawbacks, the high degree of sensitivity provided by this technique for some assays (i.e. where the amount of material being assayed is very small or where the volume of sample is very small) makes it an indispensable diagnostic tool. If these levels of sensitivity could be reached by a non-isotopic

method, then costs could be dramatically lowered and a much safer work environment could be achieved.

There is a need for a microtitre plate which provides for improved sensitivity in photometric immunoassay techniques, particularly for photon emitting immunoassays such as, chemiluminescent, bioluminescent and fluorescent immunoassays.

SUMMARY OF THE INVENTION

This invention overcomes the above mentioned difficulties by providing a microtitre plate with a multiplicity of wells or depressions with walls that are highly reflective. The plates may be formed with a reflective metal, ceramic or semiconductor coating on one or both of the side or bottom walls of the wells. Alternatively, the plates may be formed from reflective metal. Still another alternative is to place a clear microtitre plate inside a reflective plate to read the assay results. Preferred reflective metals, ceramics or semiconductors for coatings include (in a highly reflective form) aluminum, tin, magnesium, zinc, cadmium, indium, transition metals such as silver, chromium, gold, platinum and nickel, silicon, germanium, silica and alumina or alloys containing at least one of these metals. The plates may also be stamped from a highly reflective metal, for example, from bright aluminum foil.

The invention also provides an improved method of conducting a photon emitting immunoassay in the reflective plates. Enhanced sensitivity results from the use of the reflective plates.

Broadly stated the invention provides a microtitre plate comprising a plate member having top and bottom surfaces, the top surface defining a plurality of spaced, upwardly opening wells, each of said wells having side and/or bottom walls with inner and outer surface, and one or both of the side and bottom walls of said wells providing a reflective, metallized surface.

The invention also provides an improved method of conducting a photon emitting immunoassay in a multi-well microtitre plate, wherein an antigen-antibody complex is formed in the wells and photons emitted from the wells are detected by a photometric device. The improvement comprises conducting the immunoassay in a microtitre plate having a reflective metallized surface on one or both of the side or bottom walls of the wells to reflect photons emitted from the wells into the photometric device.

It should be understood that the term "wells", as used herein and in the claims, in association with microtitre plates, is meant to include both depressions having only a bottom wall (ex. shallow, round bottom depressions), and generally cylindrical wells, having both side and bottom walls. Generally cylindrical wells typically have round, flat or conical bottom walls. The side walls are typically vertical, but could vary, for example as conical or fluted side walls.

It should also be understood that the term "walls" as used herein and in the claims is meant to include the inner or outer surfaces of the wells, regardless of the well shape. Thus, the term wall, when used in association with a depression shaped well, refers to its rounded surface, although the depression does not in fact possess discrete side and bottom walls.

The phrase "reflective, metallized", as used herein and in the claims, is meant to include highly reflective surfaces produced from shiny metallic materials, for instance, aluminum, tin, transition metals, ceramics and semiconductors (all in a highly reflective form), as distinct from surfaces that are merely light scattering due to glassy or glossy properties.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The microtitre plates in accordance with the present invention are preferably produced by coating standard multi-well microtitre plates with a reflective,

metallized coating on at least a portion of the inner or outer side or bottom walls of the plates. Alternatively, the plates according to this invention are formed by stamping the wells into a reflective metal, such as bright aluminum foil. Still another alternative is to place a standard clear microtitre plate containing the assay inside a second microtitre dish having a reflective metallized coating on the inner side and/or bottom wells.

The reflective metallized coatings are preferably metal coatings because they are highly reflective and inexpensive to apply. However, ceramic or semiconductor materials may be applied as highly reflective coatings in assay applications demanding an inert surface or a surface with particular immobilization qualities.

If a clear,transparent microtitre plate is used, the coating may be provided on the inner side and/or bottom walls of the plates. Alternatively, with a transparent microtitre plate, the outer side and/or bottom walls of the plates are coated. If an opaque, coloured plate is used, the coating is provided on the inner side and/or bottom walls. The particular areas coated will vary with the particular assay technique and photometric plate reading equipment which is to be used. For instance, for bottom read plates, the bottoms of the wells may be left uncoated. Bottom read plates may include a reflective lid or plate cover for use in the actual reading equipment. Top read plates, which are most commonly used, are preferably coated on both the bottom and side walls to maximize the advantages of the reflective coating.

The walls of the microtitre plates may be shaped to maximize the utility of the reflective coating. For example, the walls may be curved (ex. rounded or parabolic) or facetted to maximize upward reflections of photons into the photometric detecting equipment.

State of the art coating techniques for example physical vapour deposition, chemical vapour deposition or electroless deposition, may be used. Physical vapour

deposition techniques include sputtering, magnetron sputtering, vacuum deposition and ion plating.

The coating is applied to a thickness such that the walls of the plate are no longer transparent to light, but are highly reflective of light.

Microtitre plates which are coated on the outside walls with the metallized reflective coating are preferred to minimize immobilization problems encountered in the assay techniques. An outer reflective coating preserves the inner wall surface (typically polystyrene) for which most immunoassay techniques have been designed. If the inner walls are coated with the metallized reflective coating, the assay technique may be altered to overcome any immobilization problems. Alternatively, a clear, inner coating of a plastic such as polystyrene may be provided on the walls themselves to avoid toxicity or immobilization problems with the metal coating. Reflective ceramic or semiconductor coatings may also be advantageously used to overcome toxicity or immobilization problems.

Shiny metals can be used for the reflective metallized coating, for example, aluminum, tin, magnesium, zinc, cadmium, indium, transition metals such as silver, nickel, gold, platinum and chromium or alloys of these or other metals. Thin reflective coatings of ceramics, such as alumina and silica, or semiconductors such as silicon and geranium, may also be used. Aluminum is particularly preferred since it does not interfere significantly with the assay techniques. The particular coating material or alloy chosen will vary with the assay technique to be performed in the wells.

Immunoassay techniques are well known in the art. The metallized reflective plates of the present invention are advantageously used in colorimetric immunoassays such as ELISA, to enhance the sensitivity of the readings off the plates. However, the plates are particulary useful in photon emitting immunoassays, including chemiluminescent, bioluminescent and fluorescent immunoassays. Such assays

are described in detail in the literature, see for example, L.J. Kricka and T.J.N. Carter, Clinical and Biochemical Luminescence, Marcel Dekker, New York (1982); L.J.Kricka et al., Analytical Applications of Bioluminescence and Chemiluminescence, Academic Press, New York (1984); and N. Monji and A. Castro, Conjunction of Haptens and Macromolecules to Phycobili Protein for Application in Florescence Immunoassay, Reviews on Immunoassay Technology, S.B.Pal (ed), Vol 1, Chapman and Hall, New York (1988).

If the plates used in photon emitting assays have a metallized reflective coating on the outer walls of the otherwise transparent plates, the assays may be conducted without alteration. However, if the coating is on the inner walls of the plate, and immobilization or toxicity problems are encountered with the metal coating, the assay technique should be modified to include a first step of coating the inner walls with an adherent plastic film. A reflective coating of ceramic or semiconductor material may also be used. These latter coatings might also be applied, in a clear form, over the reflective coating.

The invention is further illustrated by the following non-limiting examples.

Example 1

This example illustrates the preparation of a metallized microtitre plate in accordance with the present invention. A standard clear flat bottomed polystyrene microtitre plate (obtained from Corning) was coated by magnetron sputtering with aluminum metal as follows:

Magnetron Sputtering Conditions:

Equipment - Perkin Elmer 4410
Target - 99.999% Aluminum
Power - 1kW
Time - 20 min
R.P.M. - 3
Coating Thickness - 4000 Angstroms
Base Pressure - 2 X 10^{-7} Torr
Cathode/Substrate Distance - 65 mm

Working Gas - Argon

Working Gas Pressure - 20 mT

The plates were oriented on the substrate table such that either the insides of the individual wells and the top side of the plate or the outsides of the individual wells and the bottom side of the top of plates were metallized (line of sight coating). The coating thickness on the flat portions of the plates coated at normal incidence was 4000 Angstroms. On the inside vertical walls of the wells, the coating thickness varied from 4000 Angstroms at the top to about 500 Angstroms at the bottom (the aluminum coating was not transparent at the bottom).

Example 2

The two plates coated in accordance with the procedure set forth in Example 1 (i.e. metallized reflective coating on the inside or outside side and bottom walls of the wells) were tested both biologically and physically to demonstrate utility for immunoassays and to evaluate for reflectivity.

a) Reflectivity Tests

The reflectivity of the each of the plates was compared to the reflectivity of standard clear, white and black microtitre plates using a Nanospec AFT reflectometer. The instrument was standardized against an aluminized optically flat silicon wafer (coated under the conditions set forth in Example 1). Data was collected as a percentage of the standard. The results were as follows:

Standard	100%
Plate, metallized inner walls	98%
Plate, metallized outer walls	96%
Plate, clear polystyrene	9.0%
Plate, white polystyrene	7.5%
Plate, black polystyrene	4.0%

The metallized plates in accordance with the present invention were clearly much more reflective than the clear or opaque, coloured plates. This is in part due to the lack of scattering and absorption of light in the

metallized plates relative to the clear and opaque, coloured plates. This demonstrates that in any photon emitting assay, the metallized plates will result in a greater capture of emitted photons since photons not directed at the detector initially will be redirected with minimal loss, even after multiple reflections within the plate.

b) Biological Tests

A unit of alkaline phosphatase enzyme was serially diluted to extinction (from 10^0 to $10^{9)}$. Samples from dilutions were placed in individual wells of a metallized microtitre dish (coated as in Example 1, inner side and bottom walls) and a normal clear polystyrene microtitre dish. All wells were precoated with bovine serum albumin to minimize enzyme deactivation through adsorption. The microtitre dishes were then placed into a photon counting camera chamber and exposed to the enzymes substrate, p-nitrophenyl phosphate. Photons from the action of the enzyme on the substrate were counted if they reached the camera lens system. Emitted photons were counted from both plates simultaneously. It was found that the metallized plates resulted in the detection of 10 times more photons than did the non-metallized plate. This suggests that luminescent/florescent types of assays will be at least 10 times as sensitive or require 10 times less sample if the metallized plate is used.

All publications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practised within the scope of the appended claims.

CLAIMS:

1. A microtitre plate comprising:

a plate member having top and bottom surfaces, the top surface defining a plurality of spaced, upwardly opening wells, each of the wells having side and/or bottom walls with inner and outer surfaces; and

one or both of the side and bottom walls of the wells providing a reflective, metallized surface.

2. The microtitre plate as set forth in claim 1, wherein the side and/or bottom walls of the wells are formed from a reflective metallized material or are provided with a reflective metal coating on the inner or outer surfaces of the well walls.

3. The microtitre plate as set forth in claim 1, wherein the side or bottom walls of the wells are formed from a clear material and a reflective metallized coating is provided on the inner or outer surfaces of the well walls.

4. The microtitre plate as set forth in claim 1, wherein the side or bottom walls of the wells are formed from an opaque material and a reflective metallized coating is provided on the inner surfaces of the well walls.

5. The microtitre plate as set forth in claim 2, wherein the reflective metallized coating is selected from the group consisting of reflective aluminum, tin, magnesium, zinc, cadmium, indium, transition metals, ceramics and semiconductors, or alloys containing at least one of these metals.

6. The microtitre plate as set forth in claim 2, wherein the metal material or coating is reflective aluminum.

7. The microtitre plate as set forth in claim 3, wherein the coating is reflective aluminum.

8. The microtitre plate as set forth in claim 4, wherein the coating is reflective aluminum.

9. A bottom read microtitre plate as set forth in claim 1, comprising:

a plate member having top and bottom surfaces, the top surface defining a plurality of spaced, upwardly opening wells, each of the wells having side and bottom walls with inner and outer surfaces;

a lid member having top and bottom surfaces covering the upwardly opening wells;

one or both of the side walls of the wells and the lid member providing a reflective, metallized surface; and

the bottom walls being substantially transparent.

10. The microtitre plate as set forth in claim 9, wherein the side walls and lid member are formed from a reflective metal material or are provided with a reflective metallized coating selected from the group consisting of reflective aluminum, tin, magnesium, zinc, cadmium, indium, transition metals, ceramics and semiconductors, or alloys containing at least one of these metals.

11. The microtitre plate as set forth in claim 10, wherein the metal material or coating is reflective aluminum.

12. In a method of conducting a photon emitting immunoassay in a multi-well microtitre plate, wherein an antigen-antibody complex is formed in the wells and photons emitted from the wells are detected by a photometric device, the improvement comprising:

conducting the immunoassay in a microtitre plate having a reflective metallized surface on one or both of the side or bottom walls of the wells to reflect photons emitted from the wells into the photometric device.

13. The method as set forth in claim 12, wherein the reflective surface is a reflective metallized coating on the inner or outer surfaces of the well walls, said coating being selected from the group consisting of reflective aluminum, tin, magnesium, zinc, cadmium, indium, transition metals, ceramics and semiconductors.

14. The method as set forth in claim 13, wherein the reflective surface is an aluminum reflective surface on the inner or outer surfaces of the well walls.

AMENDED CLAIMS

[received by the International Bureau on 22 August 1994 (22.08.94), original claims 1-4 amended; claims 9-11 deleted; claims 12-14 amended and renumbered as claims 9-11; other claims unchanged (2 pages)]

1. A microtitre plate comprising:

a plate member having top and bottom surfaces, the top surface defining a plurality of spaced, upwardly opening wells, each of the wells having side and/or bottom walls with inner and outer surfaces; and

the bottom walls, and optionally the side walls, of the wells providing a reflective, metallized surface on the inner surface of the walls.

2. The microtitre plate as set forth in claim 1, wherein the wells are formed from a reflective metallized material or are provided with a reflective metal coating on the inner surface of the well walls.

3. The microtitre plate as set forth in claim 1, wherein the wells are formed from a clear material and a reflective metallized coating is provided on the inner surface of the well walls.

4. The microtitre plate as set forth in claim 1, wherein the wells are formed from an opaque material and a reflective metallized coating is provided on the inner surface of the well walls.

5. The microtitre plate as set forth in claim 2, wherein the reflective metallized coating is selected from the group consisting of reflective aluminum, tin, magnesium, zinc, cadmium, indium, transition metals, ceramics and semiconductors, or alloys containing at least one of these metals.

6. The microtitre plate as set forth in claim 2, wherein the metal material or coating is reflective aluminum.

7. The microtitre plate as set forth in claim 3, wherein the coating is reflective aluminum.

8. The microtitre plate as set forth in claim 4, wherein the coating is reflective aluminum.

9. In a method of conducting a photon emitting immunoassay in a multi-well microtitre plate, wherein an antigen-antibody complex is formed in the wells and photons emitted from the wells are detected by a photometric device, the improvement comprising:

conducting the immunoassay in a microtitre plate having a reflective metallized surface on the inner surface of the bottom walls, and optionally on the inner surface of the side walls, of the wells to reflect photons emitted from the wells into the photometric device.

10. The method as set forth in claim 9, wherein the reflective surface is a reflective metallized coating on the inner surface of the well walls, said coating being selected from the group consisting of reflective aluminum, tin, magnesium, zinc, cadmium, indium, transition metals, ceramics and semiconductors.

11. The method as set forth in claim 10, wherein the reflective surface is an aluminum reflective surface on the inner surface of the well walls.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 94/00158

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 B01L3/00 G01N21/03

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,91 04482 (PARK PHARMACEUTICALS) 4 April 1991 see page 1, line 3 - line 12; claims 8-10 see page 7, line 10 - page 8, line 16	1-3,9,12
Y	see page 14, line 17 - line 27 see page 14, line 9 - line 16; figure 6 --- -/--	5-7,10, 11,13,14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 1994	22.06.94

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 94/00158

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 8718, Derwent Publications Ltd., London, GB; AN 87-125114 & JP,A,62 066 141 (SUMITOMO) 25 March 1987 see abstract & PATENT ABSTRACTS OF JAPAN vol. 11, no. 261 (P-609) (2708) 25 August 1987 & JP,A,62 066 141 (SUMITOMO) 25 March 1987 see abstract	5-7,10, 11,13,14
X	DATABASE WPI Week 8620, Derwent Publications Ltd., London, GB; AN 86-129702 & SE,A,8 404 141 (WALLAC OY) 21 February 1986 see abstract	1,4,8,12
A	WO,A,89 12838 (WALLAC OY) 28 December 1989 see page 3, paragraph 3; figure 2 see page 4, line 11 - line 16	1,12 9
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E	EP,A,0 589 691 (WALLAC OY) 30 March 1994 see page 2, line 36 - line 52 see page 3, line 15 - line 25; figures	1,9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...formation on patent family members

International application No.
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